

REMARKS

The specification has been amended to insert the required SEQ ID NO identifiers associated with the listed sequences, as requested by the Office. The Sequence Listing has been revised to correct the discrepancy between the amino acid sequence shown in Figure 4 of the application and the sequence submitted as SEQ ID NO:2 with the Sequence Listing as filed on October 16, 2006. A revised Sequence Listing in computer readable and paper form is being submitted herewith, together with a verification statement to fulfill the requirements of 37 C.F.R. §1.821-1.825. The amendment to the specification and the present Sequence Listing submission contain no new matter in compliance with 37 C.F.R. §1.821(g).

The specification has been amended to include all the data contained within the Protein Data Bank entry codes 1GFS, 1FXS and 1BSV (including crystal parameters and structural coordinates), which was explicitly incorporated by reference in the instant specification (see page 24 and page 34 of the specification). A similar amendment to the specification to include the information contained in the Protein Data Bank was made during prosecution of parent application, USSN 09/373,432, now U.S. 6,459,996. The specification has also been amended to remove the references to Tables 1 and 2.

Claims 1, 6, 31-32, 34-35, 37, 39, 42, 44 and 45 have been amended. Claims 2, 5, 7, 33, 36, 38 and 41 are cancelled; claims 3-4, 30, 36-38, 40, and 43 are reiterated. Claims 8-29 were previously cancelled. Claims 46-54 have been added. Upon entry of the amendment, claims 1, 3-4, 6, 30, 32 and 34-35, 37,39-40 and 42-54 will be pending. No new matter has been added.

Claims 1 and 6 were amended to incorporate the limitations of claims 31 and 7, now cancelled. Claims 32, 39 and 42 have been amended to correct their dependencies in view of the claim cancellations made herein. Support for new claims 46-52 can be found, *e.g.*, at page 24 and page 34 of the specification.

The claim amendments and cancellations made herein are for the purpose of expediting prosecution of the instant application. Applicants do not acquiesce to the rejections made by the Office, and reserve the right to pursue the canceled subject matter in one or more continuing applications.

Information Disclosure Statement

On pages 2-3 of the Office action, the Office has requested copies of the references cited in the Information Disclosure Statement (IDS) filed on July 29, 2002. Filed herewith, please find a copy of each of the references cited in this IDS, as requested by the Examiner. A copy of the 1449 form filed on July 29, 2002 is also submitted herewith.

Claim for Domestic Priority

On pages 3-4 of the Office Action, the Office has objected to Applicants' claim of the relationship between the instant application and the prior filed application, U.S. Serial No. 09/373,432, filed on August 13, 1999. The Office asserts that:

A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the matter not disclosed in the prior-filed application. (Office action at page 3, paragraph 8.)

In particular, the Office points out to a one-amino acid discrepancy between the amino acid sequence shown in Figure 4 and the amino acid sequence submitted as SEQ ID NO:2 with the Sequence Listing filed on October 16, 2006. In response, Applicants submit herewith a new Sequence Listing revised to correct the discrepancy between the two sequences, thus cancelling the new matter. Accordingly, the present application is a proper divisional of USSN 09/373,432. No change to the claimed relationship between these two applications is needed.

Objections to the Specification/Informalities

The Office has objected to the following informalities in the specification and prior Information Disclosure Statements.

References

On pages 4-5 of the Office action, the Office has stated, the listing of references in the specification at pp. 25-34 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper. (Office action at page 4, paragraph 9.)

Applicants submit that the references listed in the specification at pp. 25-34 have been previously listed in the Information Disclosure Statement filed with the Office on July 29, 2002. A copy of each of the references cited in the IDS is submitted herewith. Review and consideration of these references is respectfully requested.

Figures

The figures filed on October 29, 2004 have been corrected in are now in accordance with 37 CFR 1.84(u)(1).

Title

The title of the invention has been amended as suggested by the Examiner, and now recites "Crystal of GDP-Fucose Synthetase Polypeptide."

Deletion of Reference to "Table 1" and "Table 2" in the Specification

The specification has been amended on pages 21 and 23 to delete reference to "Table 1" and "Table 2."

Support for SEQ ID NO:2

The Office action states that,

based on the specification amendment filed on 10/16/06, it appears applicant's intended showing of support for SEQ ID NO:2 is Figure 4, "coli_GFS." However, it is noted that the sequence of SEQ ID NO:2 and that shown in Figure 4, "coli_GFS" appear to be inconsistent as SEQ ID NO:2 appears to have a deletion of Val197 relative to the sequence of "coli_GFS" and is thus not supported by the sequence of Figure 4, "coli_GFS."

Applicants have amended the sequence of SEQ ID NO:2 to be consistent with that shown in Figure 4, "coli_GFS." Therefore, this objection has been obviated.

Applicants respectfully submit that the objections to the specification and IDS submission have been met. Reconsideration and withdrawal of these objections is respectfully requested.

Claim Objections

On pages 5-6 of the Office Action, the Office has objected to the certain claims. Each of the grounds for these rejections is addressed below.

On page 5 of the Office Action, the Office has objected to claim 7 in its recitation of “The composition of claim 6.” Claim 7 has been cancelled in view of the claim amendments made herein, thereby obviating this rejection.

On page 5 of the Office action, the Office has objected to claims 34, 44, and 45, and has suggested that, to substantially improve claim form, claim 34 should be amended to recite “diffracts x-rays at a resolution,” and claims 44 and 45 should be amended to recite “diffracts x-rays according to the structural coordinates.” Applicants have amended these claims, thus obviating this objection.

On pages 5-6 of the Office action, the Office has objected to the recitation of “the crystal comprises an active site” as recited in claim 35. As suggested by the Examiner, the claim has been amended to recite “the GFS comprises an active site.”

The above claim objections have been obviated by the amendment and cancellation of the claims made herewith. Reconsideration and withdrawal of these objections is respectfully requested.

Sequence Compliance

In order to perfect sequence compliance, Applicants have been amended the specification to insert the required “SEQ ID NO” identifiers and corrected the Sequence Listing submission of October 16, 2006 to change SEQ ID NO:2 to be consistent with the sequence shown in Figure 4, “coli_GFS.” A revised Sequence Listing in computer readable and paper form is being submitted herewith. The amendment to the specification and the present Sequence Listing submission contain no new matter in compliance with 37 C.F.R. §1.821(g).

Rejection of Claims 5-7, 33-34, 36-38, 41 and 44-45 under 35 U.S.C. §112, Second Paragraph

In paragraph 17 of the Office Action, the Office has rejected claim 5-7, 33-34, 36-38, 41, and 44-45 under 35 U.S.C. 112, second paragraph, as allegedly being “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Each of the grounds for this rejection is addressed individually below.

(a) To expedite prosecution of the instant application, claim 5 has been cancelled, without prejudice or disclaimer, thereby obviating the Office's rejection.

(b) Claim 6 has been amended, without prejudice or disclaimer, to delete the reference to "a second chemical species," thereby obviating the Office's rejection. Claim 7 has been cancelled.

(c) As to the rejection of claims 33, 41, 44 and 45 as confusing in the recitation of "the crystal has diffraction data according to Table 1," claims 33 and 41 have been cancelled and claims 44-45 have been amended to clarify that the coordinate information is a characteristic of the protein crystal, as suggested by the Office.

(d) The rejection of claims 33 and 41 as being indefinite in the recitation of "Table 1" and "Table 2" is now moot in view of the cancellation of these claims.

(e) Claim 36 has been cancelled, thereby obviating the Office's rejection.

(f) The rejection of claim 37 as not having sufficient antecedence has been met by amending this claim to depend from claim 35.

(g) The rejection of claim 38 as not having sufficient antecedence has been met by amending this claim to depend from claim 37.

(h) The Office has rejected claims 44-45 as being indefinite in the recitation of "Protein Databank entry code 1GFS" in claim 44 and "Protein Databank entry code 1FXS or 1BSV" in claim 45. According to the Office, "[i]t is well-known in the art that the data represented by a Protein Databank entry code is subject to possible modification and thus is not constant. As such, a skilled artisan would not be apprised of the metes and bounds of the claim by referencing structural coordinates of the respective PDB entry."

Applicants respectfully traverse this aspect of the rejection. As evidences by Exhibits A-C, submitted herewith, showing the history of deposition and release dates for the Protein Databank entry codes 1GFS, 1FXS and 1BSV demonstrate only one date of deposition and release for each of these entry codes, thus these entry codes have not been subject to "possible modification" as alleged by the Office. To clarify the meaning of these claims, the specification has been amended to incorporate the deposited coordinates, which was incorporated by reference at page 24 and page 34 of the specification. Any further amendments, if any, appear to have been made for formatting purposes.

Accordingly, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph, are respectfully requested.

Rejections of Claims 31-34, 36, 38, 40-41, and 43-45 under 35 USC § 112, First Paragraph

New Matter

In paragraph 18, the Office has rejected claims 31-34, 36, 38, 40-41, and 43-45 are rejected under 35 U.S.C. 112, first paragraph, for allegedly containing new matter.

While Applicants do not concede to any aspect of the Office's stated reasons for rejection of claims 31-34, 36, 38, 40-41, and 43-45, this aspect of the rejection has been met in view of the claim amendments and cancellations made herein. Each of the grounds for this rejection is discussed individually below.

(a) The Office appears to object to claims 31-34 and 44 as the disclosure allegedly "would not appear to support a genus of any GFS crystal from any source having the recited unit cell parameters, space group symmetries, and structural coordinates." Claims 31-32, 34 and 44, as amended herein, are directed to crystalline forms of *E. coli* GDP-fucose synthetase having the structural parameters specified. Claim 33 has been cancelled. Therefore, in view of the claim amendments and cancellations made herein the source of the GFS crystal is *E. coli* as disclosed in the instant specification.

(b) Regarding the Office's rejection of claim 36, this claim has been cancelled, thus obviating this aspect of the rejection.

(c) Regarding the Office's rejection of claim 38, this claim has been cancelled, thereby rendering this rejection moot.

(d) Regarding the Office's similar position with respect to claims 40-41, 43 and 45 as allegedly not supporting "a genus of GFS crystals from any source having the recited unit cell parameters, space group symmetries, and structural coordinates," this aspect of the rejection has been met by specifying in each of claims 40, 43 and 45 that claimed crystals are from *E. coli* GFS and have the structural parameters specified, thereby obviating the Office's rejection. Claim 41 is presently cancelled.

As acknowledged by the Office, the specification discloses working examples and detailed structural parameters and coordinates for three different crystals of *E. coli* GFS, namely the apo enzyme, the *E. coli* GFS in complex with NADP+ and *E. coli* GFS in complex with

NADPH. The pending claims, as amended herein, specify the source of the enzyme used in generating the crystals to be from *E. coli*, thereby obviating the new matter rejection.

Accordingly, reconsideration and withdrawal of this new matter rejection is respectfully requested.

Written Description

In paragraph 19, claims 1-7 and 30-45 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

According to the Office:

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In general, for a genus of crystals to be adequately described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein and any molecule(s) bound to it, (2) the space group, and (3) the unit cell dimensions of the crystal.

This rejection has been met by the claim amendment and cancellation made herein. As described below in more detail, Applicants submit that the claims, as presently pending, provide sufficient structural and functional features in common associated with the crystal structure of *E. coli* GDP-fucose synthetase, alone or in complex with its co-factors, NADP+ and NADPH, to satisfy the written description requirement. In particular, claim 1 (from which now pending claims 3-4, 6, 30-32, 34-38, 40, 42 and 45 depend from) are directed to a crystalline *E. coli* GDP-fucose synthetase, alone or in complex form, characterized by having the particular structural parameters disclosed by the three working examples disclosed in the present specification. The genus of GFS crystals encompassed by these claims does not have substantial variation, since all must have unit cell parameters chosen from:

- a) GFS having unit cell parameters of $a=104.2 \text{ \AA}$ and $c=74.9 \text{ \AA}$;
- b) GFS in complex with NADP+ having unit cell parameters $a=104.2 \text{ \AA}$ and $c=75.1 \text{ \AA}$;
and
- c) GFS in complex with NADPH having unit cell parameters $a=104.3 \text{ \AA}$ and $c=74.9 \text{ \AA}$.

Alternatively, as specified by newly added claims 46-53, a crystalline *E. coli* GDP-fucose synthetase (GFS) having space group P3₂21 and comprising the amino acid sequence of SEQ ID NO:2, wherein the crystalline GFS is selected from the group consisting of:

- a) a crystalline GFS having unit cell parameters $a = 104.2 \text{ \AA}$, $b = 104.2 \text{ \AA}$ and $c = 74.9 \text{ \AA}$;
- b) a crystalline GFS in complex with NADP⁺ having unit cell parameters $a = 104.2 \text{ \AA}$, $b = 104.20$ and $c = 75.1 \text{ \AA}$; and
- c) a crystalline GFS in complex with NADPH having unit cell parameters $a = 104.3 \text{ \AA}$, $b = 104.3 \text{ \AA}$ and $c = 74.9 \text{ \AA}$.

The specification discloses working examples and detailed structural parameters and coordinates for three different crystals of *E. coli* GFS, namely the apo enzyme, the *E. coli* GFS in complex with NADP⁺ and *E. coli* GFS in complex with NADPH. The three crystal forms disclosed have the same space group (P3₂21) and almost identical unit cell parameters for the three crystals disclosed, namely, $a = 104.2 \text{ \AA}$, $b = 104.20$ and $c = 74.9 \text{ \AA}$; $a = 104.2 \text{ \AA}$, $b = 104.20 \text{ \AA}$ and $c = 75.1 \text{ \AA}$; and $a = 104.3 \text{ \AA}$, $b = 104.3 \text{ \AA}$ and $c = 74.9 \text{ \AA}$. Applicants submit that the teachings of McPherson et al. (1990) *Eur. J. Biochem* 189:1-23 regarding the alleged high unpredictability of the crystallization art are not relevant to the instant case as the claims are directed to the three representative structures of GFS protein disclosed in the present application having very similar crystal forms (in terms of space group and unit cell parameters). Thus, the specification provides sufficient species within the presently claimed genus to comply with the written description requirement.

Applicants respectfully submit that the scope of claims as presently pending is commensurate with the *E. coli* GFS crystal species disclosed in the specification. Additionally, the claims in their present form impose almost identical structural parameters as those specified by hypothetical claim 1 exemplified in case 4 of the “Trilateral Project WM4 Comparative Studies in New Technologies: Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims” released in November 2002 (“the Trilateral Report”). The USPTO indicated in the Trilateral Report that hypothetical claim 1 would meet the written description requirement because the crystal structure of the protein is provided in the claim by specifying the cell unit dimension. More specifically, claim 1 in case 4 of the Trilateral Report is directed to a crystalline form of a known protein P, and reads as follows: “A crystalline form of protein P having unit cell dimensions of $a=4.0\text{nm}$, $b=7.8\text{nm}$, and $c=11.0\text{nm}$.” At pages 8 and 66 of the

report, the hypothetical specification of case 4 is described as including, *inter alia*, that the inventors have newly produced a stable crystalline form of protein P and that the description gives experimental data with explanations of how to make the crystals. The Trilateral Report, at page 67, referring to the claim of case 4, states that “the claim complies with the written description requirement because the **structure** of protein P is provided.” (emphasis added).

Like the hypothetical claim 1 presented in case 4 of the Trilateral Report, the pending claims are directed to a crystalline form of a specific known protein (*i.e.*, *E. coli* GFS), which was characterized in the art prior to the filing date in terms of its structure and function. Also similar to the hypothetical claim 1 presented in case 4, instant claim 28 recites the unit cell dimensions of the crystal. The present specification discloses, *inter alia*, that the inventors had newly produced a crystalline form of *E. coli* GFS, provided *E. coli* GFS sequence information, experimental data with explanations on how to make the crystals, and the three-dimensional structures of a crystalline form of the *E. coli* GFS polypeptide. Thus, Applicants respectfully submit that for at least the reasons above, the specification amply provides written description for the crystalline form of the *E. coli* GFS polypeptide as presently set forth in the claims.

As to claims 6 and 54, these claims are directed to crystals of *E. coli* GFS comprising, or consisting of, the amino acid sequence of SEQ ID NO:2 having the space groups specified. Applicants submit that the specification provides more than sufficient examples of crystals in complexed and uncomplexed form with the space groups provided by the claims.

In sum, the scope of the aforementioned genus encompassed by the claims does not have substantial variation in view of the claims’ precise structural parameters specified by the claims. Given the defined scope of the claims, Applicants respectfully submit that the specification provides ample number of species having a common attribute to show that the applicants were in possession of the claimed crystals. In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejections under 35 U.S.C. § 112.

Rejection of Claims 1-7 and 30-45 under 35 U.S.C. §112, First Paragraph

Enablement

In paragraph 20 of the Office Action, claims 1-7 and 30-45 are rejected under 35 U.S.C. 112, first paragraph, because “the specification, while being enabling for: 1) crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters $a=104.2 \text{ \AA}$ and $c=74.9 \text{ \AA}$ and space group

symmetry P3₂21 or P3₁21 (p. 21); 2) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP⁺ having unit cell parameters $a=104.2 \text{ \AA}$ and $c=75.1 \text{ \AA}$; and 3) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters $a=104.3 \text{ \AA}$ and $c=74.9 \text{ \AA}$, does not reasonably provide enablement for all GFS crystals as broadly encompassed by the claims."

The present rejection has been met as applied to independent claims 1 and 46 (and their dependencies), which are directed to crystalline forms of *E. coli* GFS having the space group and unit cell parameters specified. These claims are commensurate in scope with exemplary claim 1 of case 4 of the Trilateral Report, which was deemed by the USPTO to satisfy the enablement requirement. More specifically, the Trilateral Report states that claims to a crystalline form of a polypeptide (e.g., like exemplary claim 1 of case 4) satisfy the enablement requirement, if the specification teaches how to make the claimed crystals and if one skilled in the art could use the claimed crystal without undue experimentation (see the Trilateral Report at page 67 and case 4 of the Trilateral Report at page 66). The instant specification discloses how to make the claimed composition, *e.g.*, starting in the specification at page 21 up through page 24, detailed experimental conditions are disclosed providing structural parameters and coordinates for three different crystals of *E. coli* GFS, namely the apo enzyme, the *E. coli* GFS in complex with NADP⁺ and *E. coli* GFS in complex with NADPH. The three crystal forms disclosed have the same space group (P3₂21) and almost identical unit cell parameters for the three crystals disclosed, namely, $a = 104.2 \text{ \AA}$, $b = 104.20$ and $c = 74.9 \text{ \AA}$; $a = 104.2 \text{ \AA}$, $b = 104.20$ and $c = 75.1 \text{ \AA}$; and $a = 104.3 \text{ \AA}$, $b = 104.3 \text{ \AA}$ and $c = 74.9 \text{ \AA}$. The claims depending from claims 1 and 46 further specify features from the claimed crystals, *e.g.*, the amino acid sequence (claim 30), resolution (claim 34), amino acid residues comprising the GFS active site (claims 35 and 37-38), among others. Accordingly, the breadth of these claims, as amended or newly added herein, is commensurate in scope with the teachings in the specification.

As to claims 6 and 54, these claims are directed to crystals of *E. coli* GFS comprising, or consisting of, the amino acid sequence of SEQ ID NO:2 having the space groups specified. Applicants submit that the specification provides more than sufficient examples of crystals in complexed and uncomplexed form with the space groups provided by the claims.

With respect to the state-of-the-art, the disclosure describes and demonstrates methods for successfully crystallizing three working examples of the claimed *E. coli* GFS, alone or in

complex form, all of which have the same space group (P3₂21) and almost identical unit cell parameters. Once the crystallization conditions are established, one of ordinary skill in the art could have practiced the claimed invention, which, as discussed above, is directed to the very specific crystals generated following the conditions disclosed in the specification, by routine experimentation. Therefore, Applicants submit that following the teachings of the specification, one of ordinary skill in the art would have been able to generate crystals of *E. coli* GFS having the structural information encompassed by the claims by simply following the teachings of the specification.

The Office Action cites to Branden *et al.* ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999), Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995), and Kierzek *et al.* (*Biophys Chem* 91:1-20, 2001), and other references in support of the allegation that the state of the art for making a protein crystal at the time of the invention was filed was highly unpredictable. As an example, the Office cites to Kierzek *et al.* (*Biophys Chem* 91:1-20) as providing evidence that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically *established* for each protein to be crystallized."

Applicants traverse the Office's position with respect to the relevance of Kierzek *et al.* and the other cited references to the presently claimed invention. Applicants had disclosed (and optimized) in the present application several crystallization conditions of *E. coli* GFS, alone or in complex form, all of which have the same space group (P3₂21) and almost identical unit cell parameters. The Office is reminded that the claims require the *E. coli* GFS crystals to have the space unit and parameters specified, or the space unit and the *E. coli* GFS amino acid sequence specified. Not only had the *E. coli* GFS polypeptide been successfully crystallized at the time of filing present application, but also the three dimensional structure of *E. coli* GFS had been resolved. The above-cited references are not relevant to the present application as the successful crystallization of three forms of *E. coli* GFS had been performed and conditions for effecting the crystallization were disclosed in the instant application.

In view of the disclosure of the specification and the knowledge in the field of protein crystallography at the filing date, undue experimentation would not be required to make and use the subject matter covered by the claims. Applicants, therefore, respectfully request

reconsideration and withdrawal of the rejections of claims 1-7 and 30-45 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the enablement requirement.

Rejection of Claims 1-3, 5, 31, 35 and 37-38 under 35 U.S.C. §102(a)-(b)

In paragraphs 21-23 of the Office Action, the Office has rejected claims 1-3, 5, 35 and 37 as allegedly being anticipated under 35 U.S.C. §102(a) by Tonetti *et al.* (1998) *Acta Crystallogr D Biol Crystallogr* 54:684-687, "Tonetti"). Claims 31 and 38 were rejected as being anticipated (or obvious as applied to claim 38) over Tonetti *et al.*, which is applied as art under 102(b) against these claims. Claims 5 and 38 have been cancelled, thereby obviating this rejection.

The reference of Tonetti teaches a crystal of GDP-4-keto-6-deoxy D-mannose epimerase/reductase from *E. coli*, in uncomplexed form, having space group P3₂1, with cell unit parameters of $a=b=105.0 \text{ \AA}$, $c=75.6 \text{ \AA}$, wherein the amino acid sequence of the GDP-4-keto-6-deoxy D-mannose epimerase/reductase disclosed by Tonetti differs from the amino acid sequence of SEQ ID NO:2 encompassed by the claims by having two additional amino acid residues at the C-terminal end of the protein, Arg-Gly.

This rejection has been met by amending pending claims, *e.g.*, claims 1, 3-4, 30-32, 34-35, 37-38, to be directed to crystallized forms of *E. coli* GFS having the particular space group and unit cell dimensions, which differs from those disclosed by Tonetti *et al.* Similarly, newly added claim 46 (and its dependencies, claims 47-49) are directed to particular crystals of *E. coli* GFS having space group and unit cell dimensions that differ from those disclosed by Tonetti *et al.* Claim 6, as amended herein, (and its dependencies) are directed to *E. coli* GFS complexed to its co-factor, NADPH and NADP+, which was not taught by Tonetti *et al.* Claim 54 is directed to a crystallized form of *E. coli* GFS that consists of the amino acid sequence of SEQ ID NO:2, which as discussed above, is two-amino acids shorter than the amino acid sequence disclosed in the Tonetti reference.

Moreover, as acknowledged by Tonetti, the three-dimensional structure of the epimerase/reductase was not solved. Therefore, this reference also fails to anticipate (or render obvious) claims directed to crystals of *E. coli* GFS, alone or complexed to its co-factor, NADPH and NADP+, that require the structural coordinates deposited in the Protein Databank. As the title of Tonetti *et al.* states, this reference discloses preliminary crystallographic investigations of GDP-4-keto-6-deoxy-D-mannose epimerase/reductase, which "failed to provide a clear solution

for the correct orientation/location of the unknown molecule in its unit cell.” (*Id.* at page 685, right hand column). Applicants were first to solve the crystal structure of *E. coli* GFS and provides its structural coordinates, as discussed by Applicants at page 22, lines 5-9 of the specification).

The Office alleges that claim 31 is not entitled to the earliest priority date of August 13, 1998 based on USSN 60/096,452, and are rejected as being anticipated (or obvious as applied to claim 38) over Tonetti *et al.*, which is applied as art under 102(b) to these claims. Applicants traverse the Office’s position and submit that claim 31 is entitled to the earliest priority date of August 13, 1998 as the claimed subject matter is disclosed explicitly on page 24, lines 3-4 of the USSN 60/096,452. As stated above, claims directed to particular crystals of *E. coli* GFS having space group and unit cell dimensions disclosed by the instant application differ from those disclosed by Tonetti *et al.*, and thus is not anticipated by Tonetti *et al.* Claim 38 has been cancelled, thereby rendering this aspect of the rejection moot.

Therefore, the disclosure by Tonetti *et al.* fails to teach each and every limitation of the claims, and thus fails to anticipate the claims as presently pending.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. §102(a) and (b) are respectfully requested.

Rejection of Claims 31-34, 38, 40-41, and 43-45 under 35 U.S.C. §102(b)

In paragraph 31, the Office has rejected claims 31-34, 38, 40-41 and 43-45 under 35 U.S.C. §102(b) as allegedly being anticipated by Applicants’ own publication (Somers *et al.* (Structure 6:1601-1612, December 1998; “Somers”). As the basis for this rejection, the Office notes that descriptive support for these claims was allegedly not found in the earlier filed applications. Claims 33 and 41 have been cancelled, thereby obviating the Office’s rejection.

Applicants respectfully traverse the Office’s position and clarify that the remaining claims are entitled to the earliest priority date of August 13, 1998 based on USSN 60/096,452. Claims 31-32, 34, 40 and 43 are directed to crystals of *E. coli* GFS having the unit cell parameters specified. These claims are disclosed at least at page 24, lines 4-5; page 26, lines 13-14; and page 27, lines 2-3 of USSN 60/096,452, filed on August 13, 1998. The degree of resolution specified by claim 34 was disclosed in Tables 1 and 2 of USSN 60/096,452. As to claims 44-45 directed to crystal structures comprising the structural coordinates deposited in

Protein Databank entry codes 1GFS, 1FXS or IBSV, Applicants submit that these coordinates although deposited in August-September of 1998 were not released until August 17 or 26, 1999, which was after USSN 09/373,432 was filed (*i.e.*, on August 13, 1999) (see Appendices A-C, submitted herewith). Thus, the disclosure in the Somers reference is not prior art against these claims, as these claims are entitled to the earlier priority date of August 13, 1998, or there was no public disclosure of the claimed subject matter prior to the priority date.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. §102(b) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an accompanying Deposit Account authorization, please charge any deficiency to Deposit Account No. 50/2762, referencing Attorney Docket No. W2025-701740.

Respectfully submitted,
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